An Efficient Synthesis of 2,4,6-Triarylpyridines via Solvent-Free Reaction between Acetophenoneoximes and Aldehydes

Shabnam Mahernia, Mohammad Mahdavi, Mehdi Adib*

School of Chemistry, University College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran
Fax +98(21)66495291; E-mail: madib@khayam.ut.ac.ir

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Abstract: An efficient synthesis of 2,4,6-triarylpyridines is described. Heating a mixture of an acetophenoneoxime and an aldehyde under solvent-free conditions afforded Kröhnke pyridines in excellent yields. In this method acetophenoneoximes are directly used for the preparation of Kröhnke pyridines under metal-free conditions.

Key words: 2,4,6-triarylpyridines, acetophenoneoximes, aldehydes, solvent-free synthesis, cyclizations, heterocycles

The pyridine ring systems have attracted great attention due to their unique position and board range of applications in various fields such as pharmaceuticals, agrochemicals, additives, and dyes.[1–6] Their saturated and partially saturated derivatives are found in biologically active compounds and natural products including NAD nucleotides, vitamin B6, and alkaloids.[5,6]

Among pyridines, multiaryl-substituted ones, especially 2,4,6-triarylpyridines (commonly named as Kröhnke pyridines),[7] have found widespread applications as chemosensors[8] in asymmetric catalysis[9] and as photosensitizors.[10] These have been found to be useful for the synthesis of DNA binding ligands in cancer therapy.[11,12] They are useful intermediates in the synthesis of drugs, herbicides, insecticides, desiccants, and surfactants.[13] Due to their π-stacking ability along with directional H-bonding capacity, these pyridines are important building blocks in supramolecular chemistry.[14] Hence their synthesis has received considerable attention.

Since, Kröhnke's original report on the synthesis of 2,4,6-triarylpyridines (TAP),[7] several new approaches have been reported for the preparation of these pyridines.[15] More recently, much effort has been devoted to developing more efficient methods for the preparation of these pyridines, especially direct condensation reactions of acetophenones with aryl aldehydes and NH_4OAc.[16] However, many of these approaches and methods suffer from some drawbacks such as multistage processes, expensive catalysts, long reaction times, using metal oxidants, low to moderate yields of the products, and harsh or environmentally hazardous reaction conditions. Therefore, a need still exists for further development of new versatile routes for the synthesis of 2,4,6-triarylpyridine.

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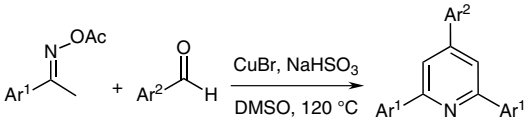
In 2011, Guan and coworkers reported a copper(I)-catalyzed coupling of oxime acetates with aldehydes which leads to the corresponding 2,4,6-triarylpyridines via a radical mechanism. The reactions were carried out in DMSO in the presence of $NaHSO_3$ as additive and at 120 °C, and the yields were in the range of 45–95% (Scheme 1).[17]



Scheme 1

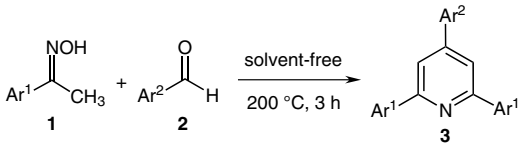
As part of our current studies on the design of efficient methods for the preparation of heterocyclic compounds from readily available starting materials,[18] we have described an efficient synthesis of TAP via a solvent-free reaction between chalcones and NH_4OAc.[19]

Knowing the chemical and pharmacological importance of the Kröhnke pyridines, herein we report a new synthesis of these pyridines. Thus, acetophenoneoximes **1** and aldehydes **2** undergo a simple 2:1 addition reaction under neutral and solvent-free conditions to produce 2,4,6-triarylpyridines **3a–s** in 85–96% yields (in respect to the acetophenoneoxime **1**). All the reactions were carried out at 200 °C and reached completion within three hours.[20] ^1H NMR analysis of the reaction mixtures clearly indicated formation of the corresponding TAP **3** in excellent yields. The results are given in Table 1.

Mechanistically it is reasonable to assume that the first step may involve nucleophilic addition of *N*-hydroxy enamine tautomer of the ketoxime **1b** on the aldehyde **2** and formation of the oxime aldol intermediate **4**, which may be dehydrated to form the α,β-unsaturated oxime intermediate **5**. This intermediate could undergo Michael addition of another ketoxime enamine tautomer **1b** to yield adduct **6**, which may be cyclized to tetrahydropyridine intermediate **7**. This intermediate may undergo removal of a hydroxylamine molecule and dehydration to produce the corresponding TAP **3** (Scheme 2).

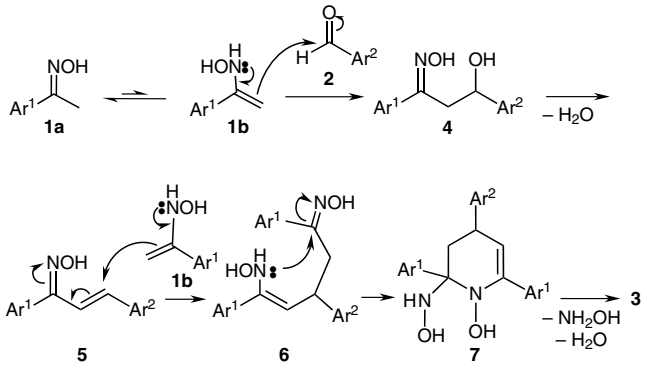
In conclusion, we have developed a new reaction for the preparation of 2,4,6-triarylpyridines which are of potential synthetic and chemical interest. Direct use of oximes in place of oxime acetates, excellent yields of the products, use of simple and readily available starting materials, neutral and solvent-free conditions without any need to use additives are the main advantages of this reaction.

Table 1 Solvent-Free Synthesis of 2,4,6-Triarylpyridines **3a–s**



Entry	Product	Ar^1	Ar^2	Mp (°C) (lit.)	Yield (%)[a]
1	**3a**	Ph	Ph	136 (136–137)[21a]	92
2	**3b**	Ph	4-$O_2NC_6H_4$	200 (202–203)[15a]	87
3	**3c**	Ph	4-MeC_6H_4	124–125 (124.5–125)[15a]	95
4	**3d**	Ph	4-$MeOC_6H_4$	101–102 (99–100)[21a]	96
5	**3e**	Ph	4-BrC_6H_4	104 (102–104)[16b]	95
6	**3f**	Ph	4-pyridyl	190–191 (187–190)[19]	90
7	**3g**	Ph	2-furyl	169 (168–170)[19]	91
8	**3h**	Ph	2-thienyl	165 (165–166)[15a]	94
9	**3i**	4-MeC_6H_4	4-MeC_6H_4	179 (178–180)[21b]	92
10	**3j**	4-MeC_6H_4	4-ClC_6H_4	201 (200.6–202)[15k]	92
11	**3k**	4-$MeOC_6H_4$	4-BrC_6H_4	165–166 (163.9–165)[15k]	94
12	**3l**	4-$MeOC_6H_4$	4-ClC_6H_4	115–116 (113.8–115)[15k]	95
13	**3m**	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	143 (143.1–144.7)[15k]	90
14	**3n**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	135–136 (136–137)[15k]	94
15	**3o**	4-$O_2NC_6H_4$	4-BrC_6H_4	>300[22]	89
16	**3p**	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	>300[22]	85
17	**3q**	4-FC_6H_4	4-ClC_6H_4	209 (209.4–210.1)[15k]	93
18	**3r**	2-pyridyl	Ph	207–208 (210–211)[23]	93
19	**3s**	2-pyridyl	4-BrC_6H_4	157–158 (154–156)[23]	89

[a] Isolated yield (in respect to the acetophenoneoxime **1**).



Scheme 2

Acknowledgement

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References and Notes

(1) Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C. I.; Yoon, S. S. *Eur. J. Med. Chem.* **2004**, *39*, 433.
(2) Enyedy, I. J.; Sakamuri, S.; Zaman, W. A.; Johnson, K. M.; Wang, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 513.
(3) Pillai, A. D.; Rathod, P. D.; Franklin, P. X.; Patel, M.; Nivsarkar, M.; Vasu, K. K.; Padh, H.; Sudarsanam, V. *Biochem. Biophys. Res. Commun.* **2003**, *301*, 183.
(4) Klimešová, V.; Svoboda, M.; Waisser, K.; Pour, M.; Kaustová, J. *Farmaco* **1999**, *54*, 666.
(5) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Vol. 5; Katritzky, A. R.; Rees, C. W.; Scriven, E. V. F., Eds.; Chapt. 6; Pergamon Press: London, **1996**, 245–300; and references cited therein.

(6) McAteer, C. H.; Balasubramanian, M.; Murugan, R. In *Comprehensive Heterocyclic Chemistry III*; Vol. 7; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Chapt. 6; Elsevier Science: Oxford, **2008**, 309–334; and references cited therein.
(7) Kröhnke, F. *Synthesis* **1976**, 1.
(8) Fang, A. G.; Mello, J. V.; Finney, N. S. *Tetrahedron* **2004**, *60*, 11075.
(9) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129.
(10) Islam, A.; Sugihara, H.; Arakawa, H. *J. Photochem. Photobiol., A* **2003**, *158*, 131.
(11) (a) Han, H.; Hurley, L. H. *Trends Pharmacol. Sci.* **2000**, *21*, 136. (b) Borman, S. *Chem. Eng. News* **2002**, *80*, 9.
(12) (a) Li, J. L.; Harrison, R. J.; Reszka, A. P.; Brosh, R. M.; Bohr, V. A.; Neidle, S.; Hickson, I. D. *Biochemistry* **2001**, *40*, 15194. (b) Siddiqui-Jain, A.; Grand, C. L.; Bearss, D. J.; Hurley, L. H. *Proc. Natl. Acad. Sci.* **2002**, *99*, 11593. (c) Kelland, L. R. *Eur. J. Cancer* **2005**, *41*, 971. (d) Chang, C. C.; Chu, J. F.; Kaol, F. J.; Chiu, Y. C.; Lou, P. J.; Chen, H. C.; Chang, T. C. *Anal. Chem.* **2006**, *78*, 2810. (e) Dexheimer, T. S.; Sun, D.; Hurley, L. H. *J. Am. Chem. Soc.* **2006**, *128*, 5404.
(13) Schaefer, P.; Hamprecht, G.; Heistracher, E.; Klintz, R.; Koenig, H.; Harreus, A.; Goetz, N.; Walter, H.; Westphalen, K.-O.; Misslitz, U. US 5733850, **1998**; *Chem. Abstr.* **1996**, *125*, 167792w
(14) (a) Wang, P.; Moorefield, C. N.; Newkome, G. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 1679. (b) Constable, E. C.; Dunphy, E. L.; Housecroft, C. E.; Kylberg, W.; Neuberger, M.; Schaffner, S.; Schofield, E. R.; Smith, C. B. *Chem. Eur. J.* **2006**, *12*, 4600. (c) Newkome, G. R.; Wang, P. C.; Moorefield, N.; Cho, T. J.; Mohapatra, P. P.; Li, S.; Hwang, S. H.; Lukoyanova, O.; Echegoyen, L.; Palagallo, J. A.; Iancu, V.; Hla, S. W. *Science* **2006**, *312*, 1782.
(15) (a) Kobayashi, T.; Kakiuchi, H.; Kato, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 392. (b) Kobayashi, T.; Kawate, H.; Kakiuchi, H.; Kato, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1937. (c) Kiselyov, A. S. *Tetrahedron Lett.* **1995**, *36*, 9297. (d) Wenkert, E.; Hanna, J. M.; Leftin, M. H. Jr.; Michelotti, E. L.; Potts, K. T.; Usifer, D. *J. Org. Chem.* **1985**, *50*, 1125. (e) Tewari, R. S.; Awasthi, A. K. *Synthesis* **1981**, 314. (f) Katritzky, A. R.; Chermprapai, A.; Patel, R. C.; Terraga-Tomas, A. *J. Org. Chem.* **1982**, *47*, 492. (g) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Am. Chem. Soc.* **1981**, *103*, 3584. (h) Palacios, F.; de Retana, A. M. O.; Oyarzabal, J. *Tetrahedron Lett.* **1996**, *37*, 4577. (i) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, 2114. (j) Cave, G. W. V.; Raston, C. L. *Chem. Commun.* **2000**, 2199. (k) Tu, S.; Li, T.; Shi, F.; Fang, F.; Zhu, S.; Wei, X.; Zong, Z. *Chem. Lett.* **2005**, *34*, 732.
(16) (a) Winter, A.; van den Berg, A. M. J.; Hoogenboom, R.; Kickelbick, G.; Schubert, U. S. *Synthesis* **2006**, 2873. (b) Shinde, P. V.; Labade, V. B.; Gujar, J. B.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2012**, *53*, 1523. (c) Khosropour, A. R.; Mohammadpoor-Baltork, I.; Kiani, F. *C. R. Chimie* **2011**, *14*, 441.
(17) Ren, Z. H.; Zhang, Z. Y.; Yang, B. Q.; Wang, Y. Y.; Guan, Z. H. *Org. Lett.* **2011**, *13*, 5394; and references cited therein.
(18) (a) Adib, M.; Sheikhi, E.; Bagheri, M.; Bijanzadeh, H. R.; Amanlou, M. *Tetrahedron* **2012**, *68*, 3237. (b) Adib, M.; Sheikhi, E.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2012**, *68*, 3377. (c) Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett.* **2011**, *52*, 3191. (d) Adib, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2011**, 619. (e) Adib, M.; Karimzadeh, M.; Mahdavi, M.; Sheikhi, E.; Mirzaei, P. *Synlett* **2011**, 834. (f) Adib, M.; Ansari, S.; Feizi, S.; Bijanzadeh, H. R. *Synlett* **2010**, 921. (g) Adib, M.; Ansari, S.; Fatemi, S.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2010**, *66*, 2723. (h) Adib, M.; Ansari, S.; Mohammadi, A.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2010**, *51*, 30. (i) Adib, M.; Ansari, S.; Feizi, S.; Asgarian Damavandi, J.; Mirzaei, P. *Synlett* **2009**, 3263. (j) Adib, M.; Mahdavi, M.; Ansari, S.; Malihi, F.; Zhu, L. G.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2009**, *50*, 7246. (k) Adib, M.; Sheibani, E.; Zhu, L. G.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2009**, *50*, 4420.
(19) Adib, M.; Tahermansouri, H.; Aali Koloogani, S.; Mohammadi, B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 5957.

(20) **General Procedure for the Preparation of 2,4,6-Triarylpyridines (3)**

A mixture of the appropriate acetophenoneoxime (2 mmol) and the appropriate aldehyde (1.2 mmol) was stirred within a sealed tube in a silicone oil bath at 200 °C for 3 h. Progress of the reaction followed by TLC monitoring. Then the reaction mixture cooled to r.t., and the residue was purified by column chromatography using *n*-hexane–EtOAc (4:1) as eluent. The solvent was removed, and the solid residue was recrystallized from absolute EtOH.

2,4,6-Triphenylpyridine (3a)

Yield: 92%; colorless crystals; mp 136 °C. IR (KBr): 3061, 3033, 2923, 1598, 1549, 1595, 1445, 1399, 1237, 1027, 873, 757, 692 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.40–7.60 (m, 9 H, 9 × CH), 7.78 (d, *J* = 8.0 Hz, 2 H, 2 × CH), 7.92 (s, 2 H, 2 × CH), 8.23 (d, *J* = 8.0 Hz, 4 H, 4 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 117.2, 127.2, 127.3 and 128.8 (4 × CH), 129.0 (C), 129.1 and 129.2 (2 × CH), 139.1 (C), 139.6 (CH), 150.2 and 157.5 (2 × C). MS (EI): *m/z* (%) = 307 (100) [M^+], 289 (6), 276 (5), 230 (68), 207 (15), 202 (44), 179 (5), 165 (6), 151 (7), 127 (6), 102 (8), 77 (28), 51 (12).

(21) (a) Lombard, R.; Stephan, J.-P. *Bull. Soc. Chim. Fr.* **1958**, 1458. (b) Huang, X. Q.; Li, H. X.; Wang, J. X.; Jia, X. F. *Chin. Chem. Lett.* **2005**, *16*, 607.
(22) Tu, S.; Jia, R.; Jiang, B.; Zhang, J.; Zhang, Y.; Yao, C.; Ji, S. *Tetrahedron* **2007**, *63*, 381.
(23) Tu, S.; Li, T.; Shi, F.; Wang, Q.; Zhang, J.; Xu, J.; Zhu, X.; Zhang, X.; Zhu, S.; Shi, D. *Synthesis* **2005**, 3045.

